

Are Local Anesthetics Needed for Local Anesthesia?

THIS issue of the Journal contains a very exciting clinical report that describes the clinical efficacy of epidural sufentanil and neostigmine in laboring women.¹ The authors examined the analgesic effects of different combinations of the two drugs without local anesthetic during the first stage of oxytocin-augmented labor. They found that a mixture of 10 μg of sufentanil with 500 μg of neostigmine seemed to be optimal based on onset, duration of action, and minimal motor block.

Efficient labor analgesia without local anesthetics may have important consequences. Research conducted over the last 20 years has resulted in excellent analgesic recipes, typically combining a very low concentration of a long acting local anesthetic with a lipid-soluble opioid. Such combinations provide near-ideal clinical conditions: low pain scores, minimal motor block (allowing ambulation), stable hemodynamics (as a result of minimal sympathetic block),² and essentially no measurable effects on obstetric outcome.³ Some might actually consider the search for better analgesic techniques to be pointless, given the efficacy of the current approaches.

However, local anesthetics are imperfect drugs. Even at low doses, their use may have catastrophic consequences.⁴⁻⁷ Moreover, although cesarean deliveries resulting from motor block are uncommon, instrumental delivery is required more frequently when regional analgesia is used. In a recent meta-analysis, the rate of instrumental delivery was almost doubled in patients receiving low dose epidural local anesthetic solutions as compared with systemic opioid analgesia.⁸

There is thus a need for analgesic drugs devoid of motor block effect. That neostigmine (the only cholinesterase inhibitor clinically available for spinal use) is one such candidate may be surprising for most of us who have followed the 15-year history of research with this agent. After experimental studies that found that muscarinic receptors and cholinergic pathways are involved in the spinal control of pain,⁹ further studies confirmed the analgesic efficacy and the safety (*i.e.*, the absence of neurotoxic complications) of intrathecal neostigmine in humans.¹⁰⁻¹⁴ However, enthusiasm rapidly declined because of the high incidence and sometimes extreme severity of nausea and vomiting.^{10,12} Because both spinally and epidurally administered drugs mainly act at the

spinal level, it is thus difficult to understand the rationale for testing epidural neostigmine. Fortunately, such skepticism did not dissuade researchers who have now shown that after epidural administration, neostigmine-induced analgesia is not associated with emetic complications, thus rehabilitating our interest in cholinergic analgesic pathways. Several trials from various countries and using different acute/pain chronic settings have confirmed that the risk/benefit ratio is excellent with epidural neostigmine.¹⁵⁻¹⁸ Although epidural neostigmine cannot be used as the sole analgesic because its potency is limited, it can provide excellent pain relief when combined with an opioid.¹⁹ Because women are believed to experience better neostigmine-induced analgesia than men,²⁰ obstetrics may represent an ideal setting for the drug. In addition, neostigmine is an old and inexpensive drug, thus facilitating its use in the current period of economic constraints.

Should the results of Roelants and Lavand'homme lead us to the routine use of epidural neostigmine in all laboring women? Certainly not. Many questions remain unanswered, and additional studies are clearly needed. One major question lies in the safety of the drug. Although there are two trials (in three animal species) demonstrating the absence of neurotoxicity,^{13,14} the drug has been used in only a few hundred human subjects and it is likely that regulatory agencies in most countries will require much more data before concluding that epidurally injected neostigmine is truly safe. An additional concern lies in the analgesic potency of the drug. In the study presented in this issue of ANESTHESIOLOGY, the analgesia produced by the epidural sufentanil-neostigmine combination was similar to that achieved with 20 μg dose of sufentanil alone. Although this is an interesting result, it is of note that the dose of sufentanil used a comparator is the ED₅₀, *i.e.*, the dose which provides adequate analgesia in only 50% of patients. Clearly, before abandoning local anesthetics, one must ensure that neostigmine can reliably provide adequate analgesia in all patients. Moreover, as this was a single-dose study, its efficacy for the whole duration of labor remains uncertain. Will the drug provide adequate analgesia when used as an infusion or will it require top-ups? Will tachyphylaxis occur? Will adverse effects occur (especially fetal effects secondary to placental transfer)²¹ after repeated administration and larger doses? Will sedation become a concern?²² Will muscle weakness become apparent after prolonged administration?¹⁰ These questions, only a few of those remaining, will require a substantial amount of added work to resolve. As with all good studies, questions remaining are more numerous than answers provided. Nevertheless, epidural neostig-

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mine provides an exciting opportunity to increase our knowledge on spinally mediated analgesia and to improve our patients' comfort.

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Anesthetic Neurotoxicity: The Collision between Laboratory Neuroscience and Clinical Medicine

ON October 10, 2003, at the 31st Annual Meeting of the Society of Neurosurgical Anesthesia and Critical Care, San Francisco, California, John Olney, M.D., Professor, Department of Psychiatry and Neuropathology, Washington University School of Medicine, St. Louis, Missouri, presented a lecture entitled "Anesthetic Neurotoxicity in Young and Aged Animals." In 1989, Dr. Olney reported in *Science* that *N*-methyl-D-aspartate antagonists such as MK801 (a well studied neuroprotectant) could produce histopathologic changes suggestive of toxicity in the brains of normal adult rats.¹ Subsequent studies have

extended and refined this work to show that many anesthetics (including N₂O) can produce what appear to be apoptotic changes, particularly the brains of very young rodents. This has raised the possibility, albeit one that is still very speculative, that even a routine anesthetic using the most routine drugs might pose a risk of neurotoxicity to the fetus, the neonate, or even the young child.

Given the obvious anxiety that such laboratory findings have produced in the minds of clinical anesthesiologists, it was not surprising that Dr. Olney's presentation was followed by an active discussion and debate. Sol Soriano, M.D., Associate Professor, Department of Anesthesia, Boston Children's Hospital, Boston, Massachusetts, was an active participant in that debate and, some months later, submitted a manuscript coauthored by K.J.S. Anand, M.B.B.S., D.Phil., Chair, Department of Critical Care Medicine, University of Arkansas, Little Rock, Arkansas, discussing and critiquing the work by Dr. Olney *et al.* In particular, Drs. Anand and Soriano asked whether or not Dr. Olney's findings are attributable to the direct effects of anesthetics or, alternatively,

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were the result of factors unlikely to be encountered clinically (e.g., high doses given over long periods, acid-based disturbances, hypoxia, starvation). In essence, what they are also asking is whether or not the published findings in rats can really be extrapolated to humans. Given the importance of the subject, the reviewers recommended that the article be published and I strongly agreed. However, I also felt that the other side of the issue needed to be heard, and hence I invited Dr. Olney and his coworkers to write the following editorial comment (although some might view it as being more akin to a "point-counterpoint" exchange between the different authors).

I personally believe that the evidence documenting the "neurotoxic"/proapoptotic effects of many anesthetics in infant rats is reasonably good. However, whether or not this can be extrapolated to humans (particularly the very young) is unknown. It would also be entirely inappropriate for anyone to suggest that anesthesiologists

should change their practice based on such work, both because we don't know if the findings apply to humans and because we have no idea what kind of change would be appropriate. In fact, neither Dr. Olney nor Drs. Anand and Soriano have made such a suggestion. The question is, however, of real importance and both Olney and coworkers and Anand and Soriano agree that much more work is needed, both in the laboratory and (hopefully) in the clinic and operating room. This is a topic that should attract the interest of far more anesthesiologists/neuroscientists. I hope that the exchange in this issue of ANESTHESIOLOGY will serve to encourage such work.

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Anesthesia-induced Developmental Neuroapoptosis

Does It Happen in Humans?

RECENTLY, we reported that transient exposure of infant rats or mice to specific classes of drugs, including those that block *N*-methyl-D-aspartate glutamate receptors, those that activate γ -aminobutyric acid_A (GABA_A) receptors, and ethanol (which has both *N*-methyl-D-aspartate antagonist and GABA_A mimetic properties), triggers widespread apoptotic neurodegeneration in the developing brain.¹⁻⁶ Because ethanol acts by a combination of *N*-methyl-D-aspartate/GABA_A mutually reinforcing mechanisms, it triggers a particularly robust neuroapoptotic response,^{2,5} which we propose can explain the neurodevelopmental disturbances associated with the human fetal alcohol syndrome. Most general anesthetics used in pediatric and obstetric medicine have either *N*-methyl-D-aspartate antagonist or GABA_A mimetic proper-

ties. Anesthetic cocktails containing drugs from both of these categories are, like ethanol, particularly effective in triggering neuroapoptosis in the developing rodent brain.⁷ The mechanisms and intracellular pathways that mediate this apoptosis response are depicted in figure 1. The window of vulnerability to these agents coincides with the developmental period of synaptogenesis, also known as the brain growth spurt period, which in mice and rats occurs primarily postnatally but in humans extends from about midgestation to several years after birth.⁸ Anand and Soriano discuss these findings and conclude that they are "certainly sound, but it may be premature to apply them to clinical settings."⁹

Anand and Soriano base much of their reasoning on a single assumption: that it requires extreme conditions for anesthetic drugs to trigger neuroapoptosis in animals. They cite a study in which Soriano *et al.*¹⁰ reproduced our finding¹ that ketamine, if given in repeated doses (extreme condition), triggers neuroapoptosis in the infant rat brain, but they rest their case on the additional finding that single-dose exposure to ketamine (mild condition) did not, in their hands, produce neuroapoptosis.¹⁰ In our original study, we did not test single-dose exposure to ketamine, but we subsequently have done so and have found (fig. 2) that a single subanesthetic dose of ketamine triggers a significant (fourfold) increase in neuroapoptosis in the infant rodent brain.¹¹ Therefore, in responding to Anand and Soriano, we must

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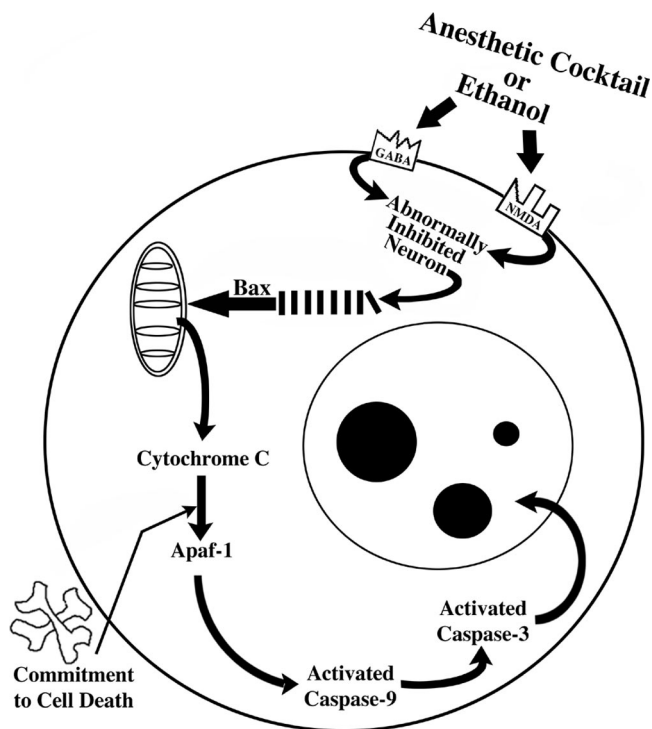


Fig. 1. The mechanism of cell death triggered by ethanol and related drugs involves translocation of Bax protein to mitochondrial membranes,¹⁵ where it disrupts membrane permeability, allowing extramitochondrial leakage of cytochrome c, followed by a sequence of changes culminating in activation of caspase-3.^{16,17} The specific steps in the upstream pathways through which the signal is relayed from the cell surface γ -aminobutyric acid_A (GABA_A) and *N*-methyl-D-aspartate (NMDA) receptors to Bax protein remain to be identified. We propose that the steps causing the cell to become abnormally inhibited precede and are separate from, but interactive with, the series of steps leading to Bax translocation (represented as a row of dominos). When the first domino is toppled, the reaction progresses down the line until it arrives at Bax protein and triggers Bax translocation to the mitochondrial membrane. If methods can be developed for stabilizing one or more dominos, thereby arresting the chain reaction before the Bax protein step, the suicide signal will not be activated. Arresting this chain reaction is an important research goal, as it may allow anesthetic drugs to put neurons to sleep without accidentally triggering a cell suicide signal.

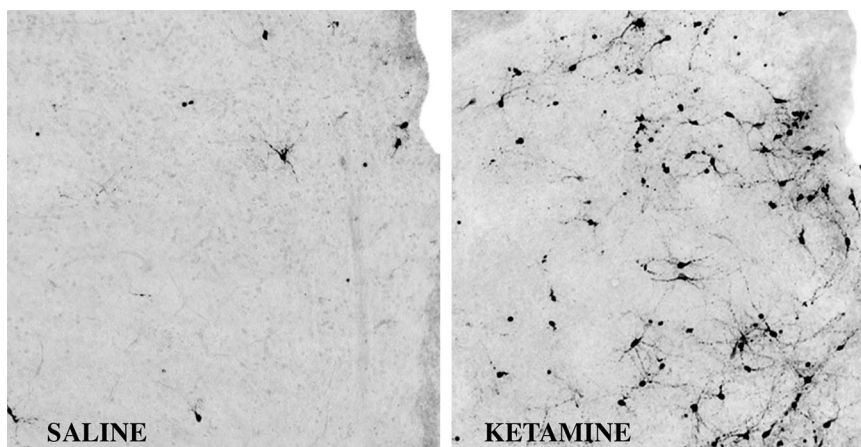


Fig. 2. In this study¹¹ we exposed P7 infant mice to a single subcutaneous injection of saline or ketamine at 10, 20, 30, or 40 mg/kg and at 5 h posttreatment counted neurons showing caspase-3 activation in the brain. We found a dose-dependent increase in apoptotic neurodegeneration in the ketamine *versus* saline pups, which was statistically significant at 20, 30, and 40 mg/kg, but marginally nonsignificant at 10 mg/kg. The brain sections depicted here are from the caudate nucleus and are representative of the rate of neuroapoptosis (neurons showing caspase-3 activation) following saline or ketamine at 40 mg/kg. At this dose, the number of apoptotic neurons in the caudate nucleus of ketamine-treated pups was 4.3 times higher than in litter-matched controls, a difference significant at the $P > 0.0001$ level. In

separate groups of infant mice we obtained arterial blood samples by cardiac puncture at periodic intervals (0, 15, 30, 60, 120, 180, or 240 min) following ketamine at 40 mg/kg. Throughout this period, blood gases remained within normal limits, including arterial oxygen saturation, which fluctuated from a low of 97 percent to a high of 99 percent.

degeneration in the infant rodent brain, the acute cell death that ensues is not apoptotic. It is excitotoxic, and ultrastructurally does not resemble apoptosis.¹²⁻¹⁴ In contrast, the acute cell death response to ethanol or anesthetic or antiepileptic drugs is decidedly apoptotic and ultrastructurally does not resemble the acute excitotoxic cell death response that typifies hypoxia/ischemia.^{3,5,13,14}

Anand and Soriano propose that the adverse effects we attribute to anesthesia exposure in infant rodents can be explained by a disturbance in nutritional status. This is not a tenable argument. At the beginning of the experiment, our infant rodents have a belly full of milk (clearly visible through the abdominal wall). In a typical experiment, we treat rat or mouse pups subcutaneously, the controls with saline and the experimentals with ethanol or an anesthetic drug, and all animals are sacrificed 4 to 8 h later for histologic evaluation of the brains. Both controls and experimentals are exposed to the same degree of nutritional and maternal deprivation; both are removed from the maternal cage and are maintained at normal body temperature in a compartment separate from their mother for the duration of the experiment. There is no rational basis for invoking nutritional factors to explain the robust pattern of neuroapoptosis that consistently shows up in the experimental brains and not in the controls.

Anand and Soriano suggest that because the life span is much longer in humans than in rodents, it might require a much longer exposure time (weeks) for a toxic chemical to induce neuroapoptosis in the developing human brain compared to a brief period (hours) in the rodent brain. They cite a theoretical treatise, but no evidence, to support this conjecture. The life span argument in its fully developed form is as follows: Disruption of synaptogenesis is the proposed mechanism by which anesthetic drugs trigger neuroapoptosis. In the rodent, synaptogenesis is completed within a period of weeks, whereas in the human it is completed within a period of several years. Neurons are programmed to commit suicide if their synaptic mission is thwarted to some critical degree. It may be argued that for the rodent neuron, 2 h of disruption exceeds the critical limit, whereas for the human neuron the critical limit may be much longer. As there are other species, including nonhuman primates, that have more prolonged synaptogenesis periods, this hypothesis should be tested in such species, the sooner the better.

This brings us to the very difficult question, how can we know whether anesthetic drugs do or do not trigger neuroapoptosis in the developing human brain? Rodent data provide an imprecise basis at best, and an irrelevant basis at worst, for evaluating human risk. An important next step, therefore, would be to conduct well designed nonhuman primate studies. Serious consideration should also be given to conducting autopsy studies in which the brains of human neonates who have died on the surgical

table after prolonged anesthesia would be compared with the brains of neonates who have died from other causes in the absence of anesthesia. Obtaining the brains immediately after death would be important to ensure successful application of special stains and related assays for diagnosing acute neuroapoptosis.

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Sleeping with Uncertainty:

Anesthetics and Desiccated Absorbent

BECAUSE of my research interest in anesthetic breakdown, I am aware of cases that I would call “rumors of injury by carbon monoxide,” which is one of the products produced by the interaction of anesthetics and carbon dioxide absorbants. Some lacked documentation, and others were mired in the litigation process. Consequently, none of these rumors was ever published. Our specialty treated every instance of carbon monoxide poisoning or other kinds of anesthetic breakdown as a mere curiosity because no injury had ever been documented and reported.

In this issue of ANESTHESIOLOGY, three cases are presented where extreme reactions occurred between sevoflurane and desiccated absorbent, producing irrefutable patient injury in one case,¹ and explosion and fire in the other two.^{2,3} Fatheree and Leighton¹ describe a patient whose intraoperative pulmonary injury necessitated a prolonged intensive care unit course. Details of absorbent drying were unknown but fit the historical pattern of Monday mornings and a weekend of gas flow through the absorbent. For years, we obsessed over the theoretical risk of compound A nephrotoxicity, but we now know there is a real risk to the lungs. Although the injury can be mild,⁴ serious injury from anesthetic breakdown is no longer a rumor.

Those with a pyromaniacal bent will be interested in reading Wu *et al.*'s dramatic report,² in which an unattended anesthesia machine exploded and ignited, and the report by Castro *et al.*, in which the explosion occurred during an anesthetic.³ In the case by Wu *et al.*, the machine was located in an induction room, where prolonged gas flows through the absorbent were possible if not routine. Presumably, previously desiccated

absorbent combined with approximately 1 hour of sevoflurane and oxygen flow and culminated in the first reported explosion and actual fire outside of a research setting since the days of flammable anesthetics.⁵ The hydration status of the absorbent was also unknown in the report by Castro *et al.*, but the case was the first of the day, the anesthesia machine had not been turned off the night before, and Baralyme® (Allied Healthcare Products, Inc., St. Louis, MO), relatively high concentrations of sevoflurane, and high-flow oxygen were used.

Intraoperative explosions and fires are not new to anesthesiology. As a resident, one of my faculty mentors described an intraoperative explosion that had fatal consequences for the patient. This, too, was a dramatic story, but I felt safe and uninvolved. It was legitimate for me to be in denial because I would never have the opportunity to use ether or cyclopropane in an operating room. Decades of practice with flammable anesthetics had mandated the use of protective antistatic devices; conductive rubber and floor sweeping chains are anachronistic reminders that still linger in some operating rooms. However, in the 21st century, we must again accept that explosion, fire, and pulmonary injury are no longer rumors. Most of us will never experience (or perhaps recognize) a similar case in our careers, just as few of our forebearers experienced an ether fire or cyclopropane explosion, but we are at risk. Today, our uncertainty resides in whether or not the absorbent is dry. We must accept this risk, and work to reduce it.

These mishaps are rare. It would be unhelpful to overreact with panic or illogical responses, but we should remain sufficiently concerned and educated that we do not cower behind denial, ignorance, or apathy. Fundamental questions remain: Why don't we see this type of reaction more often? Baralyme® and sevoflurane have been used together for a long time. When desiccated Baralyme® or soda lime are used with sevoflurane, breakdown reactions always occur; however, only a narrow range of conditions can produce these dramatic, incendiary events.⁵ Although comparative studies remain unpublished, it may be more difficult for soda lime to create dangerous situations than Baralyme®, but it is clearly not impossible.⁴ Perhaps a better question is “Do milder forms of these reactions occur frequently and go unrecognized?” Other than the meltdowns, explosions, and fires, the clinical signs of moderate carbon monoxide poisoning may resemble commonly seen perianesthetic problems like confusion, headache, and nausea.⁶ If the meltdown described by Fatheree and Leighton went unnoticed, the pulmonary injury might have been

This Editorial View accompanies the following reports: Fatheree RS, Leighton BL: Acute respiratory distress syndrome after an exothermic Baralyme®-sevoflurane reaction. ANESTHESIOLOGY 2004; 101:531-3; Wu J, Previte JP, Adler E, Myers T, Ball J, Gunter JB: Spontaneous ignition, explosion, and fire with sevoflurane and barium hydroxide lime. ANESTHESIOLOGY 2004; 101:534-7; Castro BA, Freedman LA, Craig WL, Lynch III C: Explosion within an anesthesia machine: Baralyme®, high fresh gas flows and sevoflurane concentration. ANESTHESIOLOGY 2004; 101:537-9.

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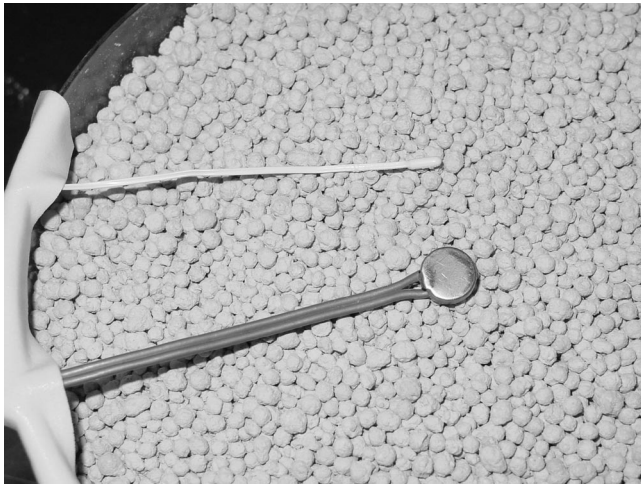


Fig. 1. This figure shows two different patient temperature monitors atop the absorbent in a canister. Placing the probes above the absorbent may be useful between canisters, but ideally they should be placed into the middle of the absorbent. Note the different thickness of lead wires. The probe with thicker wires created a leak that was difficult to seal, whereas the probe with thinner wires was easily sealed with foam tape.

attributed to occult aspiration of gastric acid or some other convenient diagnosis of exclusion.

These cases also suggest that ignition and pulmonary injury may be mutually exclusive events. One may need to distinguish between incipient fires,⁷ with pulmonary injury and extreme heat but no ignition, and the two cases of actual fires in which flames resulted. It is likely that patients absorb flammable and presumably toxic gases, preventing fire at the cost of pulmonary injury.

In all of these cases, Baralyme[®] was used, and desiccation was likely but unproven. Theoretically, we already know that stopping prolonged dry gas flow should prevent absorbent desiccation. Realistically, we can't watch the absorbent 24/7, and the possibility of absorbent desiccation before placement in anesthesia machines has never been ruled out. We know that we can avoid these dangerous chemical reactions by using absorbents devoid of strong bases. Unfortunately, recent literature is mixed about the ability of absorbents lacking strong bases to absorb carbon dioxide adequately in all situations.⁸ Strong bases were originally included in absorbents because they enhanced carbon dioxide absorption, but definitive modern comparative studies are lacking. Of course, water inhibits these chemical reactions, but water can evaporate. Nonvolatile inhibitors of anesthetic breakdown exist but have not been evaluated extensively.⁹

We need to learn more about the toxic and flammable chemicals produced by sevoflurane breakdown. Is it just fumes from the hot plastic? Or does formaldehyde cause the reported injuries?^{1,5} Anesthetic breakdown monitors can be developed, but will we use them? Carbon monoxide is produced by the breakdown of all modern

anesthetics, and we already have carbon monoxide sensors that work in the presence of anesthetics.^{10,11} But until our specialty demands this technology, no company will have incentive to build monitors that incorporates it. Color change occurs during absorbent desiccation,^{12,13} but improvements will be necessary before becoming a clinically useful indicator. As suggested by Fatheree and Leighton, perhaps today's best monitor, available in every operating room, is to place a temperature probe into the absorbent during every case. The use of a patient monitor for absorbent temperature is demonstrated in figures 1 and 2. Most patient monitors typically work up to 50°C. If the temperature approaches this value,¹⁴ excessive heating from anesthetic breakdown should be suspected, and appropriate action taken. This useful, low-cost intervention is available in any operating room with nearly every modern patient monitor, regardless of manufacturer.

After a decade of study, the problems of anesthetic breakdown and solutions to these problems are still evolving. These case reports should bring them into our consciousness.

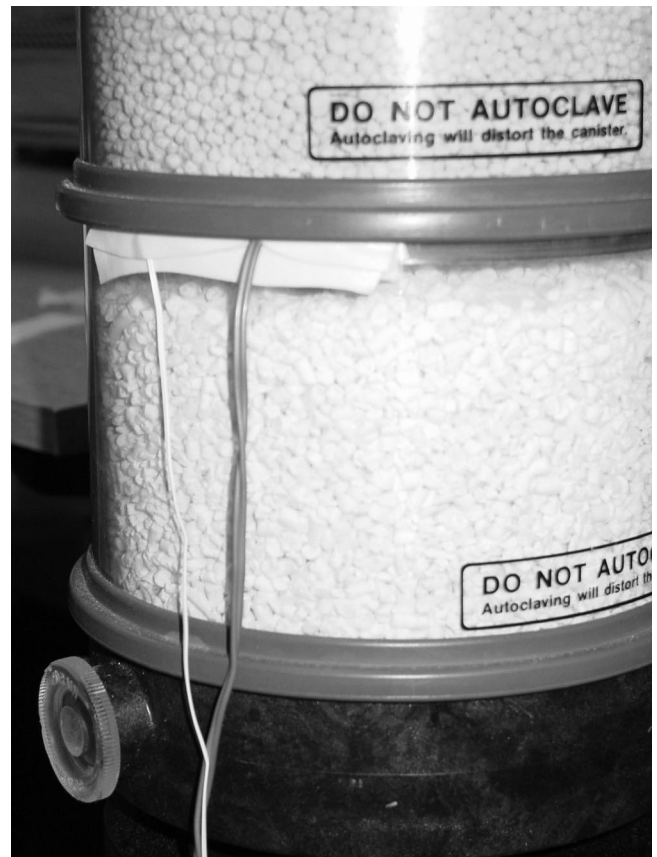


Fig. 2. This figure shows a side view of the absorbent canisters. Ideally, the temperatures of both canisters would be measured in the central parts of each canister. A small amount of foam tape (Microfoam[™], 3M, St. Paul, MN) produces an adequate air seal.

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